Successful Engraftment After Reduced-Intensity Umbilical Cord Blood Transplantation for Adult Patients with Advanced Hematological Diseases

Shigesaburo Miyakoshi, Koichiro Yuji, Masahiro Kami, Eiji Kusumi, Yukiko Kishi, Kazuhiro Kobayashi, Naoko Murashige, Tamae Hamaki, Sung-Won Kim, Jun-ichi Ueyama, Shin-ichiro Mori, Shin-ichi Morinaga, Yoshitomo Muto, Shigeru Masuo, Mineo Kanemaru, Tatsuyuki Hayashi, Yoichi Takaue, and Shuichi Taniguchi

1Department of Hematology, Toranomon Hospital; 2Hematopoietic Stem-cell Transplantation Unit, National Cancer Center Hospital; 3Department of Hematology and Rheumatology, JR Tokyo General Hospital; 4Department of Internal Medicine, Higashihiyri Hospital; and 5Department of Internal Medicine, Tokyo Metropolitan Police Hospital, Tokyo, Japan

ABSTRACT

Purpose: The purpose of this research was to evaluate the feasibility of reduced-intensity unrelated cord-blood transplantation (RI-UCBT) in adult patients with advanced hematological diseases.

Experimental Design: Thirty patients (median age, 58.5 years; range, 20–70 years) with advanced hematological diseases underwent RI-UCBT at Toranomon Hospital between September 2002 and August 2003. Preparative regimen composed of fludarabine 25 mg/m² on days −7 to −3, melphalan 80 mg/m² on day −2, and 4 Gy total body irradiation on day −1. Graft-versus-host disease prophylaxis was composed of cyclosporin alone.

Results: Twenty-six patients achieved primary neutrophil engraftment after a median of 17.5 days. Median infused total cell dose was 3.1 × 10⁸/kg (range, 2.0–4.3 × 10⁸/kg). Two transplant-related mortalities occurred within 28 days of transplant, and another 2 patients displayed primary graft failure. Cumulative incidence of complete donor chimerism at day 60 was 93%. Grade II–IV acute graft-versus-host disease occurred in 27% of patients, with median onset 36 days. Primary disease recurred in 3 patients, and transplant-related mortality within 100 days was 27%. Estimated 1-year overall survival was 32.7%. Excluding 7 patients with documented infection, 19 patients displayed noninfectious fever before engraftment (median onset, day 9). Manifestations included high-grade fever, eruption, and diarrhea. The symptoms responded well to corticosteroid treatments in 7 of 13 treated patients.

Conclusion: This study demonstrated the feasibility of RI-UCBT in adults.

INTRODUCTION

Allogeneic hematopoietic stem-cell transplantation (allo-HSCT) is a curative treatment for refractory hematological malignancies. The therapeutic benefits are attributable to myeloablative radiochemotherapy and graft-versus-leukemia effects (1), whereas the severe regimen-related toxicity (RRT; Ref. 2) limited allo-HSCT to young patients without comorbidities.

Reduced-intensity stem-cell transplantation (RIST) using a nonmyeloablative preparative regimen has been developed to decrease RRT, whereas preserving adequate antitumor effects (3–5). Different pioneering conditioning regimens for RIST have been investigated, such as those including purine analogs (3–6) and total body irradiation (TBI). Although RIST has been attempted in various diseases (5, 6), suitable preparative regimens with adequate immunosuppression have yet to be established.

Although allo-HSCT from an HLA-identical sibling is promising, only 30% of the patients have an HLA-identical sibling donor. The value of unrelated cord-blood transplantation (UCBT) was confirmed for pediatric patients (7, 8). It has seen recent application in adult patients (9). Whereas the potential graft-versus-leukemia effects by cord-blood (CB) without severe graft-versus-host disease (GVHD; Ref. 10) has been reported, current questions include whether CB provides a sufficient number of stem cells for adults and suitable graft-versus-leukemia effects.

Reduced-intensity (RI)-UCBT (11, 12) represents a promising treatment for advanced hematological malignancies. Wagner et al. (12) reported recently the feasibility of RI-UCBT for pediatric patients. However, the feasibility in adult patients remains unclear. We report 30 adult patients with advanced hematological diseases who underwent RI-UCBT after fludarabine, melphalan, and 4 Gy TBI since October 2003 at our institution.

PATIENTS AND METHODS

Study Patients and Donors. Thirty patients with hematological diseases underwent RI-UCBT at Toranomon Hospital between September 2002 and August 2003. All of the patients had hematological disorders that were incurable with conventional treatments and were considered inappropriate for conven-
tional allo-HSCT due to the lack of an HLA-identical sibling or a suitable unrelated donor, age >50 years old and/or organ dysfunction (generally attributable to previous intense chemotherapeutic or radiotherapy).

All of the patients provided written informed consent in accordance with the requirements of the Institutional Review Board.

**HLA Typing and Donor Matching.** An unrelated donor was searched through the Japan Marrow Donor Program (13) for patients without an HLA-identical sibling donor. When no appropriate donor was identified, the Japan Cord Blood Bank Network (14) was searched. CB units, which were >4 of 6 HLA-antigen matched and contained at least 2 × 10^7 nucleated cells/kg of recipient body weight before freezing were used. CB units were not depleted of T lymphocytes.

**Preparative Regimen.** The preparative regimen was composed of fludarabine 25 mg/m² on days −7 to −3, melphalan 80 mg/m² on day −2, and 4 Gy TBI in 2 fractions on day −1.

**Supportive Cares.** All of the patients were managed in reverse isolation in laminar airflow-equipped rooms and received trimethoprim/sulfamethoxazole for Pneumocystis carinii prophylaxis. Fluoroquinolone and fluconazole were administered for prophylaxis of bacterial and fungal infections, respectively. Prophylaxis of herpes virus infection with acyclovir was also given (15). Neutropenic fever was managed according to the guidelines (16, 17). Cytomegalovirus (CMV) pp65 antigenemia was monitored once a week. If positive results were identified, preemptive therapy with foscarnet was initiated. Hemoglobin and platelet counts were maintained at >7 g/dl and >10 × 10^9/liter, respectively, with in-line filtered and irradiated blood transfusions.

**Management of GVHD.** GVHD was clinically diagnosed in combination with skin or gut biopsies after engraftment. Acute and chronic GVHD were graded according to the established criteria (18, 19).

GVHD prophylaxis was a continuous infusion of cyclosporin 3 mg/kg from day −1 until the patients tolerated oral administration. It was tapered off from day 100 until day 150. If grade II-IV acute GVHD developed, 1 mg/kg/day of prednisolone was added to cyclosporin and tapered from the beginning of clinical response.

**Chimerism Analysis.** Chimerism was assessed using fluorescent in situ hybridization in sex-mismatched donor-recipient pairs. In sex-matched pairs, PCR for variable numbers of donor markers by cytogenetic and/or molecular techniques.

**RESULTS**

### Table 1 Patient characteristics (n = 30)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td></td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>14</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>3</td>
</tr>
<tr>
<td>Adult T-cell leukemia</td>
<td>5</td>
</tr>
<tr>
<td>Plasma cell leukemia</td>
<td>1</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>1</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>1</td>
</tr>
<tr>
<td>Benign</td>
<td></td>
</tr>
<tr>
<td>Severe aplastic anemia</td>
<td>4</td>
</tr>
<tr>
<td>Disease status at transplantation (malignancy)</td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>1</td>
</tr>
<tr>
<td>Refractory to previous chemotherapy</td>
<td>25</td>
</tr>
</tbody>
</table>

**Primary end points** were the rates of durable engraftment and TRM within day 100. Secondary end points were the rates of RRT, acute and chronic GVHD, infections, event-free survival (EFS), and overall survival (OS).

Acute GVHD was analyzed for engrafted patients. Chronic GVHD was analyzed for patients who survived ≥100 days.

EFS was defined as the duration of survival after transplantation without disease progression, relapse, graft failure, or death. The probabilities of OS and EFS were shown by the Kaplan-Meier method as of January 31, 2004. Surviving patients were censored on the last day of follow-up. Cox regression analysis was used to determine the effect of various variables on OS.

**Patient Characteristics.** Median age was 58.5 years (range, 20–70 years), and median weight was 52 kg (range, 38–75 kg; Table 1). All of the patients were CMV-seropositive.

The malignancies of 25 patients were refractory to cytotoxic chemotherapies except acute myeloblastic leukemia (n = 1) in first CR. The remaining 4 patients had transfusion-dependent severe aplastic anemia.

**CB Characteristics.** Twenty-four and 6 patients received 4 of 6 and 5 of 6 HLA-antigen-matched CB, respectively. Twenty-one patient CB pairs were sex-mismatched. Median infused total nucleated cell dose was 4.3 × 10^8/kg (range, 2.0–4.3 × 10^8/kg) and 0.74 × 10^8/kg (range, 0.17–2.5 × 10^8/kg), respectively.

Engraftment. Twenty-six patients [87%; 95% confidence interval (95% CI), 75–99%] achieved primary neutrophil engraftment, among whom median day of engraftment was 17.5 days (range, 10–54 days; Fig. 1). Their engraftment was durable...
without requiring readministration of Filgrastim. Two patients died of TRM within 28 days of transplant. Primary graft failure occurred in the remaining 2 patients, who underwent second RI-UCBT with the same preparative regimen and GVHD prophylaxis and achieved neutrophil engraftment and complete donor chimerism. No patients experienced a decrease in neutrophil count to <0.5 × 10^9/liter during the follow-up.

Platelet counts >20 × 10^9/liter were achieved by 16 patients (40%; 95% CI, 25–57%) on a median day of 39 days (range, 25–95 days). No other patient achieved platelet recovery until the last day of follow-up.

No significant association was found between neutrophil engraftment and either infused cell dose or HLA disparity (Table 2).

**Chimerism Analysis.** Chimerism data were obtained from all of the 30 patients. Cumulative incidence of complete donor chimerism at day 60 was 93% (95% CI, 84–100%), and median time to complete donor chimerism was 22 days (range, 13–56 days; Fig. 2). The 2 patients who died of TRM within 28 days had complete donor chimerism before neutrophil engraftment. All of the surviving patients were monitored for chimerism every 3 months, followed the cyclosporine tapering schedule from day 100 to day 150, and maintained complete donor chimerism during the follow-up even after the discontinuation of immunosuppressants.

No significant association was identified between complete donor chimerism and either infused cell dose or HLA disparity (Table 2).

**RRT and TRM.** Four patients (13%) developed grade III RRT. No patient had grade IV RRT. The most commonly involved organs were the gut and kidney (Table 3).

TRM within 100 days of RI-UCBT was 27%. Primary causes of death were interstitial pneumonitis (n = 2), acute GVHD (n = 2), gastrointestinal bleeding (n = 1), acute heart failure (n = 1), limbic encephalopathy (n = 1), and sepsis (n = 1).

**GVHD.** Grade II-IV and III-IV acute GVHD occurred in 27% (95% CI, 11–43%) and 23% (95% CI, 7.4–39%) of the patients, respectively. Median onset of grade II-IV acute GVHD was day 36 (range, day 17–66; Fig. 3).

Of the 13 patients who survived >100 days, 3 (23%) developed chronic GVHD.

**Infection.** Twelve patients developed infections: bacteremia (n = 8), invasive aspergillosis (n = 3), and pulmonary tuberculosis (n = 1). Nine of them had been treated with

---

**Table 2** Neutrophil engraftment, chimerism, and overall survival

<table>
<thead>
<tr>
<th>Neutrophil engraftment Variable</th>
<th>n</th>
<th>% (95% CI)^a</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cell dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3 × 10^7/kg</td>
<td>16</td>
<td>94% (82–100%)</td>
<td></td>
</tr>
<tr>
<td>&lt;3 × 10^7/kg</td>
<td>14</td>
<td>79% (57–100%)</td>
<td>0.25</td>
</tr>
<tr>
<td>HLA disparities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA 5/6 match</td>
<td>6</td>
<td>67% (29–100%)</td>
<td></td>
</tr>
<tr>
<td>HLA 4/6 match</td>
<td>24</td>
<td>92% (81–100%)</td>
<td>0.24</td>
</tr>
<tr>
<td>100% Donor chimerism Total cell dose</td>
<td>16</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>&lt;3 × 10^7/kg</td>
<td>14</td>
<td>86% (67–100%)</td>
<td>0.63</td>
</tr>
<tr>
<td>HLA disparity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA 5/6 match</td>
<td>6</td>
<td>83% (54–100%)</td>
<td></td>
</tr>
<tr>
<td>HLA 4/6 match</td>
<td>24</td>
<td>96% (88–100%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cell dose</td>
<td>16</td>
<td>54% (24–83%)</td>
<td></td>
</tr>
<tr>
<td>&lt;3 × 10^7/kg</td>
<td>14</td>
<td>52% (6.6–87%)</td>
<td>0.70</td>
</tr>
<tr>
<td>HLA disparities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA 5/6 match</td>
<td>6</td>
<td>63% (20–100%)</td>
<td></td>
</tr>
<tr>
<td>HLA 4/6 match</td>
<td>24</td>
<td>51% (20–81%)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

^a CI, confidence interval.

---

**Table 3** Regimen-related toxicity within 28 days (Bearman’s score)

<table>
<thead>
<tr>
<th>Score</th>
<th>Diarrhea</th>
<th>Kidney</th>
<th>CNS^a</th>
<th>Liver</th>
<th>Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>18</td>
<td>18</td>
<td>26</td>
<td>22</td>
<td>27</td>
</tr>
<tr>
<td>Grade 1</td>
<td>8</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Grade 2</td>
<td>4</td>
<td>6</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

^a CNS, central nervous system.
corticosteroids at the onset of infections. Reactivation of CMV was documented in 11 patients (37%) on a median of day 40 (range, day 13–55; Fig. 4). Eight of them had been treated with corticosteroids at the onset of CMV antigenemia. None of them developed CMV-related diseases. One patient developed hemorrhagic cystitis with adenovirus and BK virus infection.

Pre-Engraftment Noninfectious Fever. Seven patients with documented infection before engraftment were excluded from the analysis of pre-engraftment reaction (Table 4). Eighteen patients developed noninfectious fever before neutrophil engraftment (Fig. 5). Noninfectious high-grade fever often coexisted with eruption, diarrhea, and weight gain, starting on a median of day 9. Pathological examination of eruption from 8 patients revealed nonspecific inflammatory reactions and was not compatible with GVHD.

Survival. As of January 2004, a total of 11 patients remained alive. Median follow-up of the survivors and all of the enrolled patients were 238 days (range, 169–485) and 125 days (range, 26–485), respectively. Primary diseases recurred in 3 patients. Estimated 1-year OS and EFS were 32.7% (95% CI, 14.3–51.1%; Fig. 6) and 22.2% (95% CI, 5.9–38.5%; Fig. 7), respectively. Neither cell dose nor HLA disparity was associated with OS (Table 2).

DISCUSSION
Because CB contains a small amount of hematopoietic stem cells and stem cell boost or donor lymphocyte infusion is not available after UCBT, graft failure has been a major concern in adult UCBT. The present study demonstrated the feasibility of RI-UCBT for adult patients, in addition to pediatric patients (21). In this study, 26 of the 30 patients (87%) achieved durable engraftment, and 28 patients achieved complete donor chimerism by day 60, including 2 patients who died before engraftment. Interestingly, 4 patients with severe aplastic anemia, which has been associated with a high incidence of graft rejection (22), achieved complete chimerism after our reduced-intensity regimen. These findings suggest that the combination of fludarabine, melphalan, and low-dose TBI might be more immnosuppressive than conventional myeloablative regimens, creating niche for CB to engraft. Alternatively, CB may exert a strong graft-versus-host effect, making room for stable engraftment of stem cells.

Delayed hematopoietic recovery and infection during neutropenia are the significant concerns in adult UCBT. Laughlin et

![Fig. 3](image1.png)  Development of acute graft-versus-host disease (GVHD). Grade II-IV and III-IV acute GVHD developed in 27% (95% confidence interval, 11–43%) and 23% (95% confidence interval, 7.4–39%) of the patients, respectively. Median onsets of grade II-IV and III-IV acute GVHD were day 36 (range, day 17–66) and day 30 (range, day 17–44), respectively.

![Fig. 4](image2.png)  Development of cytomegalovirus reactivation. Reactivation of cytomegalovirus was documented in 11 patients (37%) on a median of day 40 (range, day 13–55).

![Fig. 5](image3.png)  Clinical course of a patient who developed pre-engraftment fever. Immune-reactions display two peaks, at around day 9 and day 18.

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>38.0–38.9</td>
<td>2</td>
</tr>
<tr>
<td>39.0–39.9</td>
<td>10</td>
</tr>
<tr>
<td>≥40.0</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day of peak body temperature</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of peak serum levels of CRP</td>
<td>Number of Patients</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>12.5–18.9</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein.

Table 4  Characteristics of pre-engraftment reaction (n = 23)
al. (23) reported neutrophil recovery in 90% of patients by a median of 27 days after UCBT, which was significantly delayed compared with allo-HSCT. The delay has been attributed to the limited cell dose in the reports on myeloablative UCBT. The median nucleated cell dose in our study (3.1 × 10^7/kg; Ref. 9) was greater than those in some reports from Western countries (2.1 × 10^7/kg; Ref. 9). The low median body weight (52 kg) in the Japanese population may favor neutrophil engraftment, whereas our results showed no association between the cell dose and engraftment in the small sample size. In the present study, median time to engraftment was 17.5 days (range, 10–54 days), which was much faster than that reported in previous studies on myeloablative UCBT (7–9). Our results were comparable with the report on adult RI-UCBT by Barker et al. (21). Their results showed neutrophil engraftment on a median of 26 days after busulfan/fludarabine/TBI 2 Gy and 9.5 days after cyclophosphamide/fludarabine/TBI 2 Gy. Whereas the reason for the difference remains unclear, these findings suggest that fludarabine-based reduced-intensity regimens enable rapid and stable engraftment.

TRM within 100 days was 27% in this study, which is lower than those reported on myeloablative UCBT (Refs. 7, 9, 24; 32–51% in pediatric patients and 56–63% in adults). Given the relatively old age (median, 58.5 years) and advanced stages of the primary diseases, our reduced-intensity preparative regimen probably decreased TRM. Our TRM within 100 days is comparable with that of 28% in adult RI-UCBT by Barker et al (21).

All of the patients tolerated our preparative regimen without grade IV RRT (Bearman’s criteria; Ref. 2). Four patients developed grade III RRT with common involvements of the gut, kidney, and liver (Table 3). We used melphalan, which has dose-limiting toxicities of the gut and liver (25). These remained mild without hepatic veno-occlusive disease. Because renal toxicities of fludarabine, busulfan, and TBI 4 Gy are reportedly minimal, the high incidence of renal toxicity might be attributable to concomitant administration of nephrotoxic agents such as cyclosporin and antibiotics. Elderly patients might be susceptible to RRT. We plan to investigate optimal dosages of cyclosporin in RIST for elderly patients. Because TBI, even at a low dose, sometimes causes significant late toxicities in the lung (22), long-term follow-up is required.

Little information on GVHD after RI-UCBT is available. In the present study, the incidences of grade II-IV and III-IV acute GVHD and chronic GVHD were 27%, 23%, and 23%, respectively, whereas some reported those to be 33–44%, 11–22%, and 0–25%, respectively, in myeloablative UCBT (7, 8, 26). There are no significant differences in the incidences of GVHD between myeloablative UCBT and RI-UCBT. This is similar to the GVHD incidences in myeloablative allo-HSCT and RIST (27). Median onset of acute GVHD was 36 days (range, 17–66 days) in the present study, which was comparable with that of myeloablative UCBT (7, 8, 26). In contrast, the achievement of complete donor chimerism and the onset of acute GVHD are delayed in RIST compared with myeloablative allo-HSCT (27, 28). CB might have a potential of intense graft-versus-host effect, allowing niche for early engraftment. The characteristics of GVHD after RI-UCBT remain to be investigated, including different organ involvements and response to immunosuppressive treatment.

Interestingly, 20 patients developed inflammatory reactions before engraftment (Table 4). These reactions included noninfectious high-grade fever, eruption, diarrhea, and jaundice, starting on a median of day 9. Because the reactions preceded engraftment (median, day 17.5), we speculated that some form of immune reaction that is not categorized as acute GVHD occurs after RI-UCBT without achieving engraftment. The pre-engraftment fever has been reported on rare occasions in previous reports of UCBT and might be similar to those observed after haploidentical transplantations. Antithymocyte globulin and corticosteroids, which have strong immunosuppressive properties, were commonly used in previous studies on UCBT (9), whereas neither was used in the present study. Immunosuppressive treatment with corticosteroids was effective for the pre-engraftment fever. These findings support that immune-mediated reactions after UCBT might manifest easily with the present regimen. The doubling time of cultured CB CD34+ cells is 7–10 days, which is several hundred-fold faster than that of cultured adult marrow cells (29). Mononuclear cells from CB display a unique cytokine profile such as comparable levels of
interleukin (IL) 2, IL-6, and tumor necrosis factor α, reduced levels of IFN-γ and IL-10, and complete absence of IL-4 and IL-5 (30, 31). Pre-engraftment fever is possibly attributable to a cytokine storm induced by massive proliferation of cells with a unique cytokine profile. Another possibility is homeostasis-driven proliferation of naive T cells in highly immunosuppressed individuals, as demonstrated in murine models (32, 33). This reaction is reportedly associated with cytokytic cytokines (32, 33). Fever as a transient response to contamination with maternal blood or cells during CB collection cannot be excluded (34). Reactivation of human herpesvirus 6 might be associated with this complication (35). If pre-engraftment fever exerts some antitumor effects, it is reasonable that patients with advanced and chemorefractory hematological diseases achieved long-term remission after RI-UCBT in the present study.

Infection is a common and significant problem in myeloablative UCBT (8, 9, 24), but little is known in RI-UCBT. The present study demonstrated that infection is also problematic in RI-UCBT. Twelve patients developed infection in this study, 9 of whom had been on corticosteroid therapy. Eight of 11 patients with CMV antigenemia had received corticosteroids. Delayed immunological reconstitution with or without GVHD, pre-engraftment fever, and corticosteroids may be risk factors for infection. Appropriate management of GVHD and pre-engraftment fever warrants additional investigation.

One-year OS was 35% in the present study, showing that some patients with advanced hematological malignancies can achieve durable remission after RI-UCBT. Contrary to our prediction, primary diseases recurred only in 3 patients. The candidates for RI-UCBT have extremely poor prognosis with conventional salvage chemotherapy. These findings suggest that RI-UCBT exerts strong antitumor activity and is promising for patients with refractory hematological malignancies without an HLA-identical sibling or an unrelated donor. In contrast, it is premature to apply RI-UCBT to low-risk diseases.

In conclusion, our study demonstrated the feasibility of RI-UCBT for adult patients with advanced hematological diseases, although the limitations included the small sample size and short follow-up. If CB is feasible for adults as an alternative stem cell source, RI-UCBT may become the choice of treatment for patients with advanced hematological diseases that are incurable with conventional treatments. RI-UCBT is particularly appealing for patients who require urgent treatments. Although RI-UCBT is currently associated with a high TRM, this study provided a rationale for continuing our clinical trials. Additional investigations need to focus on minimizing adverse effects including RRT, GVHD, and pre-engraftment immune reactions, whereas preserving graft-versus-leukemia effects.

REFERENCES
22. Deeg HJ, Aynylon ID, Harris RE, et al. Marrow transplants from unrelated donors for patients with aplastic anemia: minimum effective


Successful Engraftment After Reduced-Intensity Umbilical Cord Blood Transplantation for Adult Patients with Advanced Hematological Diseases

Shigesaburo Miyakoshi, Koichiro Yuji, Masahiro Kami, et al.


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/10/11/3586

Cited articles
This article cites 35 articles, 16 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/10/11/3586.full#ref-list-1

Citing articles
This article has been cited by 9 HighWire-hosted articles. Access the articles at:
http://clincancerres.aacrjournals.org/content/10/11/3586.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.